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ENDOTHELIUM-DEPENDENT RELAXATION IS IMPAIRED IN AORTIC RINGS FROM A RAT MODEL OF HEART FAILURE

David C Lindsay, Canwen Jiang, Francois Brunotte, Stamatis Adamopoulos, Andrew J S Coats, Bheeshma Rajagopalan, Philip A Poole-Wilson, Peter Collins.
Dept. Cardiology, National Heart & Lung Institute, London, U.K..

A functional endothelial cell abnormality may contribute to the raised systemic vascular resistance in chronic heart failure. The response of aortic rings from rats with heart failure to endothelium-dependent and -independent vasodilators was studied.
The left coronary artery was ligated with a 6-0 silk suture in 160-180g female Wistar rats (Group A), and similar sham operations performed (Group B). The surviving rats were sacrificed 3-4 months post-operatively, and the thoracic descending aorta removed. Rings of aorta were suspended in an organ bath, at a resting tension of 1g. The contraction of the rings in response to prostaglandin $F_{2\alpha}$ ($PGF_{2\alpha}$, $3x10^{-6}$M), and their subsequent relaxation to acetylcholine (ACh, 10^{-7}M&10^{-6}M) and sodium nitroprusside (SNP,10^{-7}&10^{-6}M) was measured, having elicited a satisfactory constrictor response to $PGF_{2\alpha}$. The severity of heart failure was assessed by the ratio of right ventricular weight x 1000/body weight (Group A 1.10, Group B 0.62, p<0.001). The response (±SEM) to vasoactive drugs was as follows:-

		Group A (n=9)	Group B (n=6)	
Constriction to:	$PGF_{2\alpha}$	1.4±0.1g	1.3±0.1g	(p=NS)
Relaxation to:	ACh 10^{-7}M	11±2%	33±6%	(p<0.05)
	10^{-6}M	32±6%	63±6%	(p<0.001)
	SNP 10^{-7}M	41±11%	58±15%	(p=NS)
	10^{-6}M	83±8%	83±9%	(p=NS)

Conclusion: These findings show a defect in endothelium-dependent relaxation of aortic rings to ACh in heart failure, with preserved endothelium-independent vasodilation to SNP.

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RELATIONSHIP OF ENDOTHELIN TO SYMPTOMS AND HEMODYNAMICS IN CONGESTIVE HEART FAILURE

Edward R. O'Brien, Terrence D. Ruddy, Randall A. Sochowski, Sharon Ann Kearns, Adolfo J. de Bold, University of Ottawa Heart Institute, Ottawa, Canada

Endothelin is the most potent vasoconstrictor yet identified. Congestive heart failure (CHF) is characterized by increased systemic vascular resistance (SVR) that is not fully accounted for by activation of the renin-angiotensin or sympathetic nervous systems. Therefore, we related plasma endothelin levels to dyspnea (NYHA class) and Doppler-derived hemodynamic parameters in 10 pts with chronic CHF and 11 normal volunteers. NYHA class among CHF pts varied from Class II to IV.
Supine immunoreactive plasma endothelin-1 (ET-1) activity was higher in CHF pts compared to normals (5.1 ± 6.2 pg/ml vs 0.3 ± 0.2 pg/ml, p=0.01). Similarly, atrial natriuretic factor levels were higher in CHF (324 ± 185 pg/ml vs 40 ± 36 pg/ml, p=0.0001). Cardiac index (CI) was lower (2.0 ± 0.3 l/min/M^2 vs 2.9 ± 0.5 l/min/M^2, p=0.0001) and SVR index (SVRI) was increased (2632 ± 823 dynes-sec/cm^5·M^2 vs 2144 ± 378 dynes-sec/cm^5·M^2, p=0.05) in CHF. There was no significant correlation between ET-1 and CI or SVRI. However, ET-1 tended to be higher in patients with NYHA Class IV symptoms vs those patients with NYHA Class II and III symptoms (p=0.08).
Conclusion: 1) Plasma ET-1 levels are elevated in patients with chronic CHF. 2) These increased ET-1 levels are not related to hemodynamic parameters but appear to vary with NYHA symptom class. Thus, endothelin levels may be a new hormonal marker for functional severity of CHF.

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CHARACTERIZATION OF ENDOTHELIAL FUNCTION IN PATIENTS WITH CHRONIC HEART FAILURE

Helmut Drexler, Daniel Hayoz, Thomas Münzel, Andreas M. Zeiher, Burkard Hornig, Hanjörg Just, Hans R. Brunner, Robert Zelis. Med. Klinik III, Univ. Freiburg, FRG and Div. Hypertension, Univ. Lausanne, Switzerland

Endothelial dysfunction may be involved in the impaired perfusion of skeletal muscle in patients with chronic heart failure (CHF). Accordingly, the endothelial function of conduit and resistance vessels was examined in CHF (n=9; peak-VO2 15.4±1 ml/min/kg) and normal controls (N, n=12) by infusion of acetylcholine (ACH, 10-8, 10-7, 5x10-7 M), N-methyl-mono-L-arginine (NMMA, 12 µmol/min; inhibitor of basal release of nitric oxide)(NO)and nitroglycerine (NTG, 5 nmol/min) into the brachial artery. The radial diameter (D, 5-8 cm proximal of wrist) was determined by a novel A-mode ultrasound technique (10 MHz transducer) which demonstrated a precision of ± 1 µm in extensive validation studies. Forearm blood flow (BF) was calculated from BF velocity (7.5 MHz Doppler adjerent to 10 MHz device) and cross-sectional area (+ p<.05 for N vs CHF; * p< 0.05 or more vs control).

		ACH 5x 10-7 M	NMMA	NTG
Flow (% vs control)	N/CHF	97*/ 15+	-17/-51*+	285*/83*
D (% vs control)	N/CHF	6*/ 2	-2/-1	25*/15*+

Thus, the response to ACH in conduit and resistance vessels was attenuated indicating that the receptor-mediated release of NO by ACH is blunted in CHF. Yet, the effect of NMMA was exaggerated in resistance vessels in CHF suggesting that the basal release of NO from endothelium of resistance vessels in the forearm is enhanced and may be operating at near maximal. These endothelial abnormalities may contribute to the impaired vasodilatory capacity within skeletal muscle in CHF, e.g. during exercise.

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FOREARM VASODILATION TO HYPEROSMOLAL STIMULI IS REDUCED IN PATIENTS WITH HEART FAILURE

Alan J. Bank, Spencer H. Kubo, Thomas S. Rector, M. Nicholas Burke, Cardiovascular Division, University of Minnesota, Minneapolis, MN.

Vasodilation of skeletal muscle vasculature is reduced during exercise in heart failure (HF). An increase in plasma osmolality is one of the local stimuli related to increases in blood flow during exercise. Therefore, we hypothesized that patients with HF would demonstrate decreased responses to hyperosmolal stimuli. Changes in forearm blood flow (FBF; ml/min/100 ml FAV) were measured with strain guage plethysmography following the intraarterial infusion of matched doses of isoosmolal (280 mosm/kg) and hyperosmolal (480 and 660 mosm/kg) saline and glucose solutions in 10 normal subjects (NL) and 9 HF. Baseline FBF was 2.42±1.23 in HF and 3.59± 1.47 in NL (p=0.08). The saline and glucose solutions resulted in identical dose response curves in both groups. The increase in FBF with hyperosmolal infusions as compared to isoosmolal infusions was highly significant in both groups (p<0.01). At the 480 mosm/kg dose, the FBF response tended to be less in HF than NL (2.19± 0.44 vs 3.38±0.47, p=0.08). At the 660 mosm/kg dose, the FBF response was significantly reduced in HF (4.06±0.92 vs 7.13±0.77, p<0.05). The increase in venous osmolality at the 660 mosm/kg dose was greater in HF than in NL (17.3±6.5 vs 10.0±5.8) mosm/kg, p<0.05) because the lower FBF in HF resulted in less dilution of the osmolal stimulus. Therefore, the reduced vasodilation in HF occurred despite a greater osmolal stimulus. These differences in FBF responses were not associated with differences in venous sodium, potassium, calcium or hematocrit values. We conclude that forearm vasodilation due to hyperosmolal stimuli is reduced in HF.